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Research

ANALYTICAL METHOD VALIDATION FOR DETERMINATION OF RESIDUAL TRIETHYLAMINE CONTENT IN ERTAPENEM SODIUM BY HEAD SPACE GAS CHROMATOGRAPHY

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Abstract

The analysis of residual organic solvent Triethylamine in Ertapenem Sodium, an active pharmaceutical ingredient was investigated. Ertapenem is used to treat certain serious infections, including pneumonia and urinary tract, skin, diabetic foot, gynecological, pelvic, and abdominal (stomach area) infections, that are caused by bacteria. The Headspace gas chromatography method described in this investigation utilized HP-5, 30 meter x 0.53 mm with 5.0 µm, FID detector. The injector temperature was set at 220ºC. Nitrogen was used as a carrier gas. The method was validated to be specific, linear, precise, sensitive, rugged and showed excellent recovery.

Keywords: Triethylamine, Ertapenem Sodium, Validation, Gas Chromatography

INTRODUCTION

Chromatography originated in early 1900 when Russian Botanist Mikhail S. Tswett separated plant pigments using calcium carbonate packed glass columns. It was not until midcentury that the technique was applied to develop paper chromatography, High Performance Liquid Chromatography and Gas Chromatography[1]

Chromatography helps isolate almost all components present in a mixture in pure form instead of just a single component starting with a small amount of the mixture[2] (nano grams or micro liter quantities).

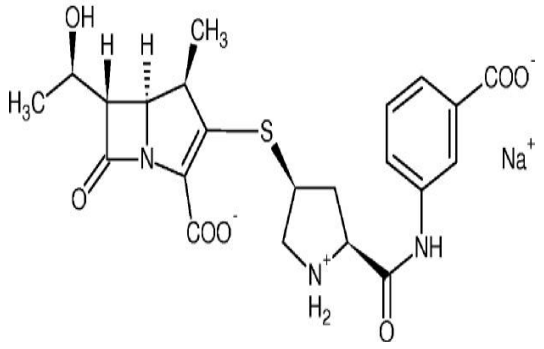
This was not possible earlier as the conventional methods were time consuming, required larger amount of sample and expensive solvents for isolation of a single component only. This important advantage contributed to the phenomenal growth and applications of different chromatographic techniques[3].

Injection Techniques:• Micro Syringes • Packed column injectors • Split/ Splitless capillary column injectors • PTV• Automated Liquid Injectors • Pyrolysers • Thermal Desorption• Sampling Valves

Columns:• Packed Columns • Fused Silica, **Detector:**• Flame Ionization Detector • Thermal Conductivity Detector • Electron Capture Detector • Mass Spectroscopic Detector• Flame Photometric Detector• Nitrogen Phosphorous Detector

The greatest impetus to the evolution of gas chromatography has been through introduction of hyphenated techniques such as GC-MS, GC-MS-MS, GC-HS, GC-FT-IR and GC-TGA-FT-IR, which have further broadened the applications range of GC[6].

DRUG PROFILE: Ertapenem sodium Molecular Formula-$C_{22}H_{24}N_3O_7SNa$ **Molecular weight:** 497.50, **Solubility-** Soluble in Water



MATERIALS & METHOD

Dimethyl sulfoxide-honey well, Triethyl amine-Merck, Piperazine anhydrous- SRL, Acetic acid-merck, Methanol Merck Isopropyl alcohol Merck Methyl acetate Alfa aesar Dichloromethane-Merck, Ethyl acetate-Merck, Benzene, Pyridine- Toluene-merck, Tetrahydrofuran-Thermo Fisher, Ethanol-merck, Diethyl ether-Merck, Cyclohexane- Scharlau, N,N-Dimethylformamide- Honeywell

Details of Instruments and Columns:

Name Of The Instrument	:	Instrument/Column Id	:	Serial Number
GC	:	SSPL-DR/HSGC/02 SSPL-CL1/GC/01	:	CN10930006 CN10902103
Analytical Balance	:	SSPL-DR/BAL/01	:	1126101745
Columns	:	SSPL-011-15	:	USE211313H

Preparation of Blank solution: Transfer 2.0 mL of diluent into a Head space vial, add 100 mg of Piperazine and immediately seal it with PTFE silicone rubber septa.

Preparation of Standard Stock Solution:

(Weigh separately for preparation of Standard Stock solution -1 & 2)

Accurately weigh and transfer about 50 mg of Triethylamine into a 50 mL volumetric flask containing 5.0 mL of diluent and dilute to volume with diluent.

Preparation of Standard Solution: (Prepare standard in duplicate as Standard solution-1 & Standard solution-2): Pipette out 2.0 mL of standard stock solution into 50 mL volumetric flask and dilute to volume with diluent.

Pipette out 2.0 mL of standard solution into six head space vials, add 100 mg of Piperazine and immediately seal it with PTFE silicone rubber septa.

Evaluation of Blank and system suitability: Place the sealed head space vials of Blank, Standard solution-1 in six (6) injections and standard solution-2 in duplicate injections as verification standard in the magazine and perform head space analysis as per the given instrumental parameter and record the peak responses. Examine the blank chromatogram for any extraneous peaks. There should be no interference from the blank at the retention time of analyte peak those was obtained from standard solution.

Preparation of Sample solution: Accurately weigh and transfer about 250 mg test sample into two separate head space vials and add 2.0 mL of diluent and 100 mg of Piperazine to each of the vials. Seal the vials immediately with PTFE silicone rubber septa.

Procedure: Place the sealed head space vials of sample preparation in the magazine and perform the head space analysis as per the given instrumental conditions

Determine the peak responses from the chromatographic report and calculate the amount of Triethylamine solvent present.

Table 12: System suitability Results:

Parameter	Result	Acceptance criteria
% RSD for Peak Area of standard solution-1	1.0	NMT 15.0
Standard agreement between standard solution-1 & 2	100.6	85 % to 115%

Acceptance criteria: The % RSD for area of Triethylamine peak in six injections of standard solution should be not more than 15.0,The standard agreement between standard solution-1& 2 should be 85% to 115%.,
Conclusion: The above results reveal that the system meets the required system suitability criteria.
Specificity: Blank Interference: Injected blank solution and checked for the peak interferences found due to blank at the retention times of Triethylamine.

Table 13: System suitability Results:

Parameter	Result	Acceptance criteria
% RSD for Peak Area of standard solution-1	0.9	NMT 15.0
Standard agreement between standard solution-1 & 2	100.6	85 % to 115%

Table 14: Results of Blank interference:

Parameter	Peak found at the RT of Triethyl amine peak (Yes/No)
Blank Solution	No

Solvents Interference: Injected separately Blank, TEA, sample solution, sample solution spiked with TEA at specification level. The specificity of method was further demonstrated by injecting listed solvents (Methanol, Ethanol, Diethyl ether, Isopropyl alcohol, Methyl acetate, Dichloromethane, Ethyl acetate, Tetrahydrofuran, Cyclohexane, Benzene, TEA, Acetic acid, Pyridine, N,N-Dimethyl formamide & Toluene) individually and by spiking test solution with mixture of solvents and evaluated the interference of other solvents.

Table 15: Results of solvent Interference:

Name of the solvent	Retention time of Triethyl amine peak in Spiked sample
Triethyl amine	10.510 min

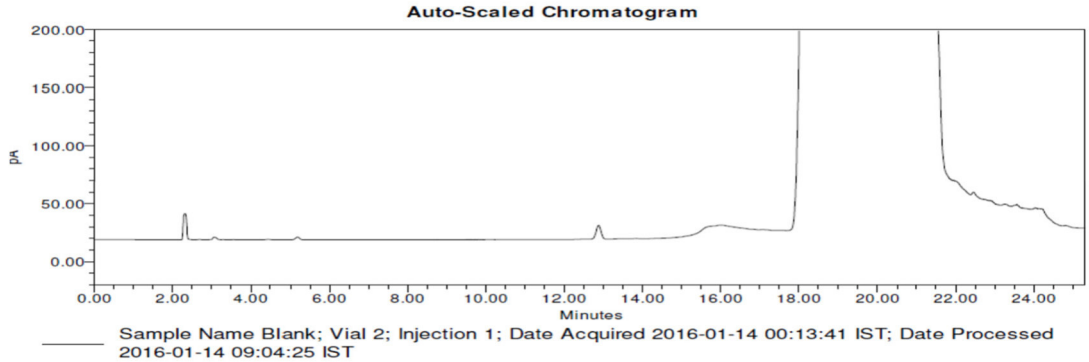


Figure 7: Typical Chromatogram of Blank

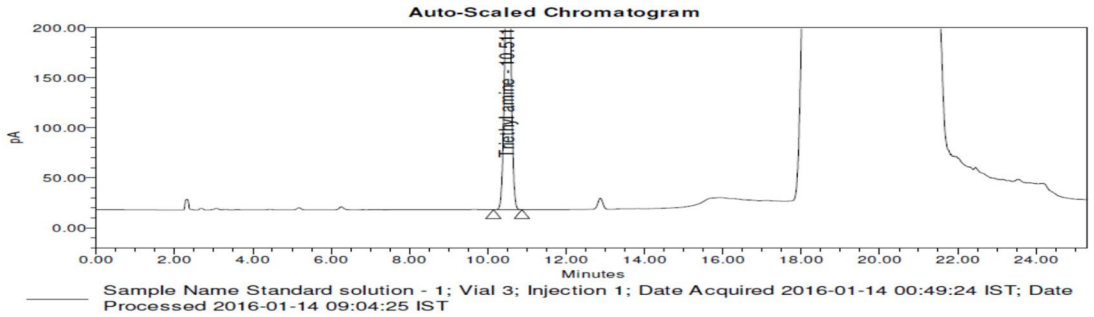


Figure 8: Typical Chromatogram of Standard

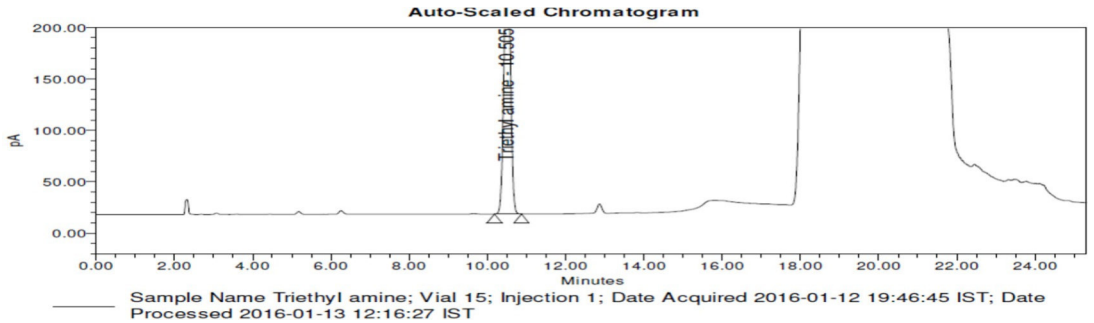


Figure 9: Typical Chromatogram of Triethylamine

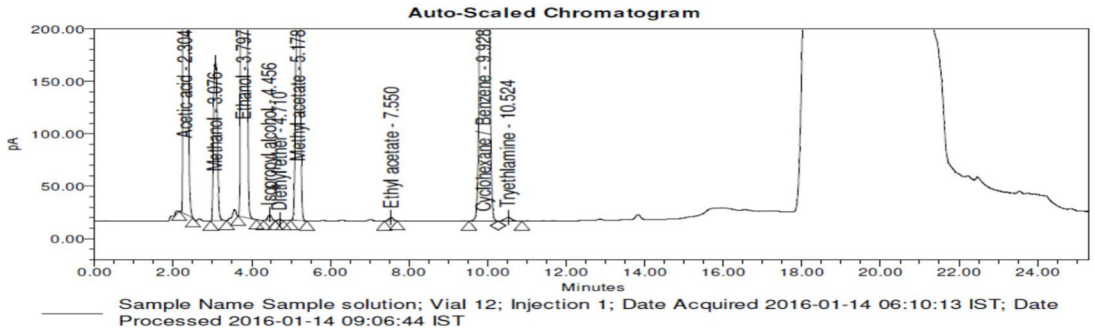


Figure 10: Typical Chromatogram of Sample (As such)

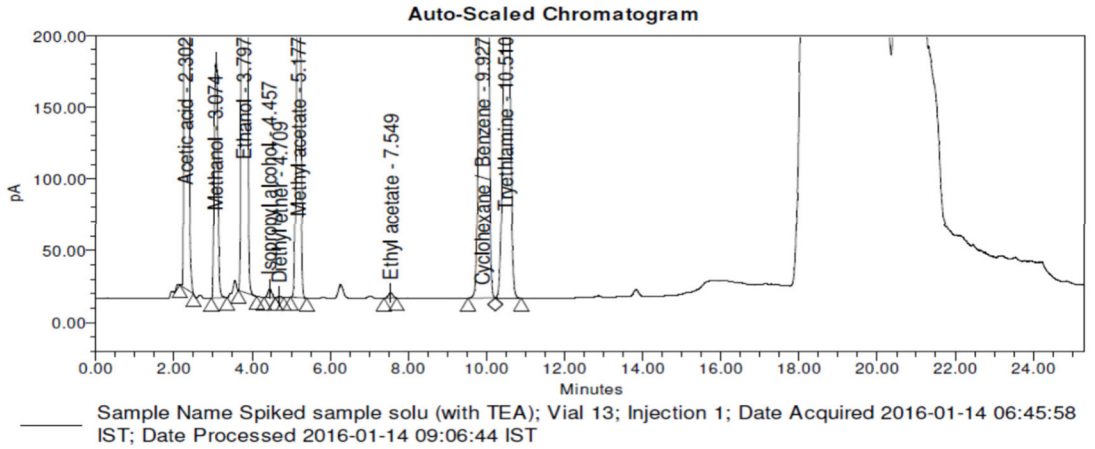


Figure 11: Typical Chromatogram of Sample Spiked with Triethyl amine

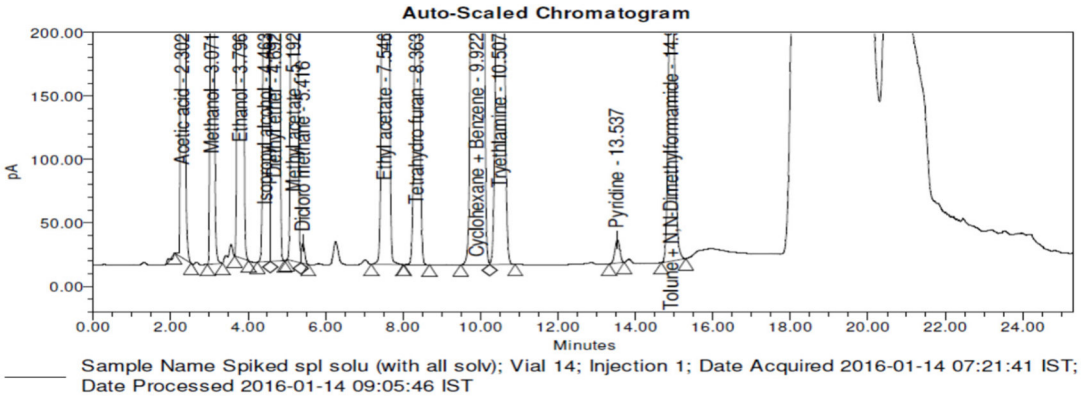


Figure 12: Typical Chromatogram of sample Spiked mixture of solvents

Acceptance criteria : The % RSD for area of Triethylamine peak in six injections of standard solution should be not more than 15.0, The standard agreement between standard solution-1 & 2 should be 85% to 115%,No interference of other solvent peaks at the retention time of Triethylamine. The blank should not show any interference at the retention time of the Triethylamine peak in the standard and sample solution.

Conclusion: No Interference was observed due to the blank at the retention time of Triethylamine in standard and sample solution. The above results reveal that the method is specific.

Precision:System Precision: Injected six replicate injections of standard solution-1 into the chromatographic system as per the test method and evaluated the system suitability and system precision parameters.

Table 16: System suitability Results:

Parameter	Result	Acceptance criteria
% RSD for Peak Area of standard solution-1	1.0	NMT 15.0
Standard agreement between standard solution-1 & 2	100.6	85 % to 115%

Table 17: System Precision Results:

S No.	Triethylamine peak area
1	2275
2	2270
3	2252
4	2290
5	2253
6	2226
AVG	**2261**
% RSD	**1.0**

Acceptance criteria: The % RSD for area of Triethylamine peak in six injections of standard solution-1 should be not more than 15.0,The standard agreement between standard solution-1 & 2 should be 85% to 115%,

Conclusion: The above results reveal that the system is precise.

Method Precision: Determined the precision by preparing the six test preparations by spiking Triethylamine standard solution at specification level and analyzed as per the test method.

Table 18: System suitability Results:

Parameter	Result	Acceptance criteria
% RSD for Peak Area of standard solution-1	1.0	NMT 15.0
Standard agreement between standard solution-1 & 2	100.6	85 % to 115%

Table 19: Method Precision Results:

Preparations	Triethyl amine Content (ppm)
1	376.83
2	357.04
3	369.81
4	377.57
5	335.35
6	351.63
Average	**361.37**
% RSD	**4.6**

Acceptance criteria: The % RSD for area of Triethylamine peak in six injections of standard solution should be not more than 15.0, The standard agreement between standard solution-1 & 2 should be 85% to 115%, The % RSD for the Triethylamine content from the six preparations of the method precision solutions should be not more than 15.0

Conclusion: The above results reveal that the method is precise.

Practical Quantitation Limit (PQL) & Practical Detection Limit (PDL):

Practical Quantitation Limit (PQL):

Injected seven replicate injections of standard solution-1 into the chromatographic system as per the test method and evaluated the system suitability and system precision parameters.

Table 20: System suitability Results:

Parameter	Result	Acceptance criteria
% RSD for Peak Area of standard solution-1	4.9	NMT 15.0
Standard agreement between standard solution-1 & 2	102.3	85 % to 115%

Table 21 : Practical Quantitation Limit (PQL) added concentration:

Name of Solvent	PQL (ppm)
Triethyl amine	160.22

Table 22: Practical Quantitation Limit (PQL) Results:

S No.	Triethylamine peak Area
1	1138

2	1151
3	1164
4	1169
5	1163
6	1179
7	1186
AVG	1164
% RSD	1.4

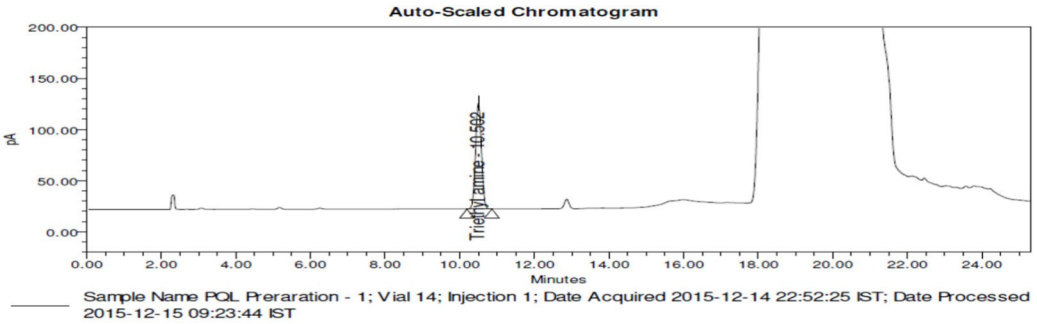


Figure 13: Typical Chromatogram of PQL

Table 23: Practical Detection Limit (PDL):

Injections	**Results**	**Acceptance criteria**
	Area	
1	388	Peak should be detectable
2	391	

Table 24: Practical Detection Limit (PDL) added concentration:

Name of Solvent	**PDL (ppm)**
Triethyl amine	52.87

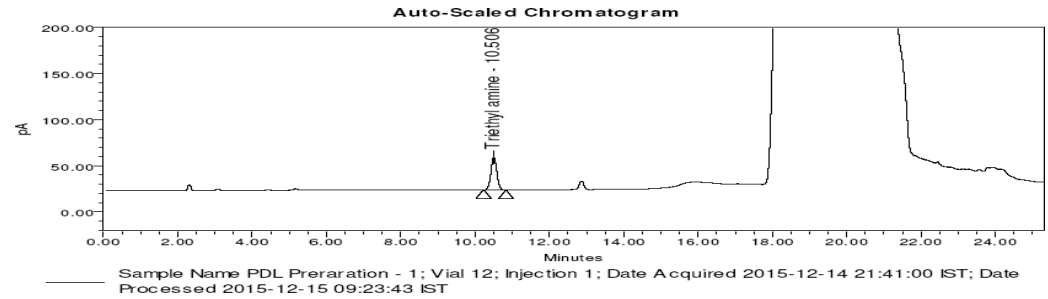


Figure 14: Typical Chromatogram of Practical Detection Limit

Acceptance criteria: The % RSD for area of Triethylamine peak in six injections of standard solution-1 should be not more than 15.0, The standard agreement between standard solution-1 & 2 should be 85% to 115%, The % RSD for area of Triethylamine peak in seven injections of PQL solution should be not more than 15.0

Conclusion: The above results reveal that the method is precise at PQL level.

Accuracy: Injected accuracy samples in triplicate at PQL and 100% of target concentration. Calculated the %

individual recovery and % mean recovery at each level.

Table 25: System suitability Results:

Parameter	Result	Acceptance criteria
% RSD for Peak Area of standard solution-1	4.9	NMT 15.0
Standard agreement between standard solution-1 & 2	102.3	85 % to 115%

Table 26: Solvents content in as such sample:

S.No	Preparation	Triethylamine (ppm)
1	**1**	1.70
2	**2**	1.70
AVG	1.70	

Table 27: Triethyl amine Accuracy Results:

Sample No.	Spike Level	Concentration found (in ppm)	Concentration added (in ppm)	Individual % Recovery	Mean % Recovery	Mean % RSD
1	PQL-1	164.23	160.22	102.5	104.2	2.0
2	PQL-2	166.05	160.22	103.6		
3	PQL-3	170.64	160.22	106.5		
1	100 %	375.13	322.05	116.5	113.7	2.8
2	100 %	355.34	322.05	110.3		
3	100 %	368.11	322.05	114.3		

Acceptance criteria

- The % RSD for area of Triethylamine peak in six injections of standard solution-1 should be not more than 15.0
- The standard agreement between standard solution-1 & 2 should be 85% to 115%
- Individual % recovery and mean % recovery value for 100% level should be in between 80 to 120.
- Report the Individual % recovery and mean % recovery value for PQL level

Conclusion: The above results reveal that the method is accurate.

Deviation: No deviations were observed.

Conclusion: The present analytical method was validated as per defined protocol and it meets thespecified acceptance criteria. Hence, it was concluded that the analytical method isspecific, precise and accurate. Hence, the present analytical method can be used for regular analysis and its intended purpose.

CONCLUSION

The current analytical method was validated according to the protocol, and it passes the acceptance criteria. Thus, it was determined that the analytical approach is particular, precise, linear, accurate, rugged, and robust. As a result, the current analytical approach is suitable for regular analysis and serves its intended function.

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